Reply to EPA Comments on Chemical RTK HPV Challenge Submission: Diethyl Sulfate

SUMMARY OF EPA COMMENTS
With Sponsor's Responses in blue

201-15002

The sponsor, the Dow Chemical Company, submitted a test plan and robust summaries to EPA for Sulfuric acid, diethyl ester (Diethyl sulfate, CAS No. 64-67-5) dated January 6, 2004. EPA posted the submission on the ChemRTK HPV Challenge Web site on February 26, 2004.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical Properties and Environmental Fate. The data provided by the submitter for physicochemical endpoints are adequate for the purposes of the HPV Challenge Program. The data provided by the submitter for photodegradation, biodegradation, and fugacity and the proposal to test for stability in water are adequate for the purposes of the HPV Challenge Program.

Response: *The Dow Chemical Company thanks EPA for their review and agreement that the data provided in combination with the proposed testing are adequate for the purposes of the HPV Challenge Program.*

2. Health Effects. The data submitted for the acute and genetic toxicity endpoints are adequate for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries. The repeated-dose, reproduction and developmental toxicity endpoints have not been satisfied for the purposes of the HPV Challenge Program. The submitter has not adequately supported the claim that exposure controls justify a reduced testing approach.

Response: *The Dow Chemical Company thanks EPA for their review. Please see detailed comments below for responses.*

3. Ecological Effects. EPA agrees with the submitter's proposal to determine ecological testing needs from the results of a proposed stability in water study.

Response: *The Dow Chemical Company thanks EPA for their review and agreement that the data provided in combination with the proposed testing are adequate for the purposes of the HPV Challenge Program.*

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA COMMENTS ON THE DIETHYL SULFATE CHALLENGE SUBMISSION

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program.

Response: *The Dow Chemical Company thanks EPA for their review and agreement that the data provided are adequate for the purposes of the HPV Challenge Program.*

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The data provided by the submitter for photodegradation, biodegradation and fugacity are adequate for the purposes of the HPV Challenge Program. EPA agrees with the submitter's approach to stability in water testing.

Response: *The Dow Chemical Company thanks EPA for their review and agreement that the data provided are adequate for the purposes of the HPV Challenge Program.*

Biodegradation. EPA located an aerobic MITI test that is equivalent to OECD TG 301 (Chemicals Inspection and Testing Institute. 1992. Biodegradation and bioaccumulation data of existing chemicals based on the CSCL Japan, Japan Chemical Industry Ecology-Toxicology and Information Center. ISBN 4-89074-101-1, page 2-101). The submitter could usefully add this information to the biodegradation robust summary.

Response: *The Dow Chemical Company thanks EPA for their review. This study will be added to the robust summary.*

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproduction/developmental toxicity)

The submitter suggests that exposure to diethyl sulfate is controlled at the site of manufacture and that "no significant exposure to consumers is anticipated to occur." The Guidance for Testing Closed System Intermediates (CSI) for the HPV Challenge Program (http://www.epa.gov/chemrtk/guidocs.htm) allows for a reduced testing protocol provided certain criteria are met. The submitter needs to document that the exposure controls are at least equivalent to CSI criteria in order for reduced testing to be acceptable for the purposes of the HPV Challenge Program.

Response: *The Dow Chemical Company thanks EPA for their review. However, The Dow Chemical Company makes no claim that diethyl sulfate is either a closed system or site-limited intermediate. No additional testing was proposed for the following reasons:*

- *Repeated dose toxicity testing data are already available as summarized for four carcinogenicity studies: two skin-painting studies, one oral gavage study, and one intravenous trans-placental carcinogenicity study. In spite of some study variances from guideline procedures, results of these studies indicate a potential for carcinogenicity, and the material is labeled accordingly. With the stringency of carcinogenicity labeling already in place, The Dow Chemical Company believes that conducting additional repeated dose toxicity testing, with the attendant animal use, will not generate additional information which would increase safety data sheet or label warnings.*

- *Manufacturer communications for safe handling of diethyl sulfate, both internal to the facilities and to external customers, recommend stringent measures to reduce the chance of worker exposure. Minimum personal protective equipment recommended are monogoggles, face shields, neoprene gloves, protective clothing, neoprene boots, and a self-contained breathing apparatus. It is advised that any spills to protective clothing should be washed as quickly as possible to prevent potential penetration. It is also recommended that diethyl sulfate be maintained in closed equipment to prevent vapor leakage, with local exhaust ventilation where leakage cannot be eliminated. The manufacturer recommends a workplace exposure limit of 1 ppm TWA. Equipment cleanup procedures recommend flushing equipment with water for up to three days to promote complete hydrolysis of diethyl sulfate to ethanol and sulfuric acid, with additional cleanup appropriate to those chemicals. With stringent worker protection policies already in place, The Dow Chemical Company believes that conducting additional repeated dose toxicity testing, with the attendant animal use, will not generate additional information that would increase safety data sheet or label warnings.*

- *Results of structure-activity relationship analysis via TOPKAT® and DEREK® confirm that diethyl sulfate is a probable carcinogen, thus supporting the results of the chronic studies. The analysis also indicated a low probability that diethyl sulfate could cause developmental toxicity, although the accuracy of that estimate could not be determined.*

- *Although no developmental toxicity/reproduction toxicity studies are available for diethyl sulfate, there is a continuous breeding protocol study available for a closely related chemical, dimethyl sulfate. The results of this study indicate a potential for dimethyl sulfate to interfere with fertility. The two chemicals demonstrate similar toxicokinetic profiles; data from in vitro hydrolysis studies show that both hydrolyze to the alcohol (methanol or ethanol) and the substituent mono-alkyl sulfate initially, with potential further hydrolysis to additional alcohol and sulfuric acid. Developmental toxicity profiles for both alcohols and the acid are well-characterized, and those data could be extrapolated to diethyl sulfate.*

For the above reasons, The Dow Chemical Company continues to plan no further testing.

Adequate data are available for acute and genetic toxicity for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries.

Response: *The Dow Chemical Company thanks EPA for their review and agreement that the data provided are adequate for the purposes of the HPV Challenge Program.*

Repeated-dose toxicity. The data from carcinogenicity studies submitted for this endpoint are not
adequate because the robust summary failed to address several important adequacy criteria. These include identification of a NOAEL and a LOAEL, presentation of hematological and clinical chemistry findings, listing of organs examined at necropsy, and other findings. If the claim for reduced testing is not supported, the combined repeated-dose/reproduction/developmental toxicity screening test (OECD TG 422) will satisfy this endpoint.

Response: *The Dow Chemical Company thanks EPA for their review. Data will be added to the robust summary. The Dow Chemical Company makes no claim for reduced testing. However, for the reasons cited above, no further testing is planned.*

Reproductive toxicity. If the claim for reduced testing is not supported, the submitter needs to provide data for this endpoint. The combined repeated-dose/reproduction/developmental toxicity screening test (OECD TG 422) will satisfy this endpoint for the purposes of the HPV Challenge Program.

Response: *The Dow Chemical Company thanks EPA for their review. The Dow Chemical Company makes no claim for reduced testing. Because of the availability of reproduction toxicity data for a similar material (dimethyl sulfate) and for potential metabolites of diethyl sulfate (ethanol and sulfuric acid),as well as low probability for reproductive effects in structure activity relationship analysis, no further testing is planned. If necessary, data for the similar material and/or potential metabolites can be added to the robust summaries, as can TOPKAT® and DEREK® results.*

Developmental toxicity. The submitter needs to provide data for this endpoint. If the claim for reduced testing is not supported, the combined repeated-dose/reproduction/developmental toxicity screening test (OECD TG 422) will satisfy this endpoint for the purposes of the HPV Challenge Program. If the claim for reduced testing is supported, the submitter still needs to provide data for this endpoint. In that case, the combined reproductive/developmental screening test (OECD TG 421) will satisfy this endpoint.

Response: *The Dow Chemical Company thanks EPA for their review. The Dow Chemical Company makes no claim for reduced testing. Because of the availability of reproduction toxicity data for a similar material (dimethyl sulfate) and for potential metabolites of diethyl sulfate (ethanol and sulfuric acid),as well as low probability for reproductive effects in structure activity relationship analysis, no further testing is*

planned. If necessary, data for the similar material and/or potential metabolites can be added to the robust summaries, as can TOPKAT® and DEREK® results.

Ecological Effects (fish, invertebrates, and algae)

EPA agrees with the submitter's proposed use of the results from the proposed stability in water study to determine the need for aquatic toxicity testing and thus reserves judgment on the need for such testing.

Response: *The Dow Chemical Company thanks EPA for their review and agreement that the results from water stability testing will be used to determine the need for further testing.*

Specific Comments on the Robust Summaries

Health Effects

Acute toxicity. The robust summary for acute oral toxicity in rats is missing the following information: a description of the method used, the range and number of doses, sex and verification of strain and a description of clinical observations. The robust summary for acute inhalation toxicity is missing the following information: a description of the method; sex and strain of rats; and a description of clinical observations. The robust summary for acute dermal toxicity is missing the following information: a description of the method; sex, strain and number of animals used; and a description of clinical observations.

Response: *The Dow Chemical Company thanks EPA for their review. Data will be added to the robust summary.*

Acute toxicity. The robust summary for acute oral toxicity in rats is missing the following information: a description of the method used, the range and number of doses, sex and verification of strain and a description of clinical observations. The robust summary for acute inhalation toxicity is missing the following information: a description of the method; sex and strain of rats; and a description of clinical observations. The robust summary for acute dermal toxicity is missing the following information: a description of the method; sex, strain and number of animals used; and a description of clinical observations.

Response: *This paragraph appears to be a replication of the previous paragraph.*

Genetic toxicity (in vitro). The robust summary for the HGPRT assay needs to include the identity and concentration of the positive control used. The cell culture conditions of the CHO cells should also be described.

Response: *The Dow Chemical Company thanks EPA for their review. Data will be added to the robust summary.*

Genetic toxicity (in vivo). The robust summaries of the two micronucleus assays need to identify the positive and negative controls. The number of males and females used should also be identified.

Response: *The Dow Chemical Company thanks EPA for their review. Data will be added to the robust summary.*

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.